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10/586,165	11/19/2007	Mitsuhiro Shikida	450104-05892	5637

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EXAMINER

PREGLER, SHARON

ART UNIT	PAPER NUMBER
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1772

MAIL DATE	DELIVERY MODE
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11/09/2011

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/586,165

Applicant(s)

SHIKIDA ET AL.

Examiner

SHARON PREGLER

Art Unit

1772

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 August 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 17-35 is/are pending in the application.
- 5a) Of the above claim(s) 23-35 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 17-22 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☒ Claim(s) 17-35 are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Response to Amendment

The Examiner acknowledges Applicant's response filed on August 23, 2011 containing amendments and remarks to the claims.

Claims 17-22 are currently under prosecution.

Election/Restrictions

Claims 23-28 have been amended from a chemical analytical apparatus to a chemical analytical method. Newly submitted claims 29-35 are directed to method of processing and chemically analyzing small droplets. Claims 23-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are directed to a method of processing and chemically analyzing small droplets. The groups are distinct because the apparatus as claimed can be used for a different process such as fluid separation and sorting.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 23-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

MAINTAINED REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blankenstein US 6,432,630 in view of Mehta et al. US 6,632,655 in further view of Ishiguro et al. JP 2003-050245 (already of record).

Regarding claim 17, Blankenstein teaches a chemical analytic apparatus (*microflow system 1, figure 1, column 12 line 62 – column 13 line 12*) which performs various kinds of processing for analyzing fluid chemically (*column 1 lines 20-30*), including:

in a condition where magnetic ultrafine particles (*magnetically stained particles 12 in sample 9, figure 1*) are mixed and contained inside a fluid (*column 3 line 65 – column 4 line 10; column 12 lines 50-60, figure 1*),

a conveyance means (*external magnet 8 proximate to flow channel 5 applies magnetic field to move magnetically stained particles to outlet 6; figure 1 column 12 lines 60-65*), wherein the fluid, to which said magnetic ultrafine particles were mixed is conveyed in another liquid (*buffers 10 & 11 enter flow channel, column 13 lines 1-5; furthermore, the magnet drives magnetic fluid to chamber 37 where it may contain washing fluid or reagents for reactions or analysis; column 17 lines 9-13*), for processing of chemical analysis, due to attraction by (*field generating means with a magnet 8, column 13 lines 1-5*) said magnetic ultrafine particles to the magnetic field of the conveyance means (*attracted to magnet, figure 6*); and

a processing means (*includes Blankenstein's step of selectively magnetically staining cells in a fluid containing target (cancer) cells and other cells, guiding a flow of the fluid containing the cancer cells through a flow channel in such a way that one cancer cell at the time passes a cross-section of the flow channel, positioning the flow channel in a magnetic field that is substantially perpendicular to a longitudinal axis of the flow channel so that magnetically stained cancer cells residing in the flow channel are deflected in the direction of the magnetic field, column 3 line 65 - column 4 line 10*) by which operations for processing of chemical analysis are performed one by one in the process in which the fluid to which said magnetic ultrafine particles were mixed is conveyed by said conveyance means (*column 12 line 62 – column 13 line 12, figure 1*), wherein

plural kinds of the fluid (*there is fluid containing target cells, fluid containing other cells, and suggested two buffers 10 & 11*) to which said magnetic ultrafine particles are mixed and of only the fluids are provided,

and said processing means is covered by thin plates (*Si wafer where flow channel 5 is etched onto column 13 lines 40-50 & figure 2*) at least on four side faces and a bottom face (*at least the bottom and side faces are the Si plate, See figure 2*) so as to be filled with another liquid,

Blankenstein further teaches a chemical reactive operation itself or part of the operation is performed by uniting the optional fluid in another compartment (*collection chamber 37 may contain a liquid or reagent fluid for further chemical reactions or analysis, column 17 lines 9-13*) with the another fluid out of said plural kinds arranged in the other small compartments. (*See figure 1, 6-7, column 1 lines 20-30, column 3 line 65 – column 4 line 10, column 12 lines 50-65, column 13 lines 1-15 & 40-50, column 16 lines 35-45*).

Blankenstein does not explicitly teach that the fluid is in the form of droplets. However, the term “droplet” does not add weight to the apparatus claim since “Expressions relating the apparatus to contents thereof during an intended operation are of no significance in determining patentability of the apparatus claim.” Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969). Furthermore, “[i]nclusion of material or

article worked upon by a structure being claimed does not impart patentability to the claims.” See *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935) (as restated in *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963)) (see MPEP § 2115).

Blankenstein does not teach said processing means is separated by bulkheads projecting into the processing means from the top side into plural small compartments which communicate with each other includes small compartments separated by plural bulkheads, and said plural kinds of the droplets to which said magnetic ultrafine particles were mixed and of only the droplets are arranged in said small compartments, and an optional droplet to which said magnetic ultrafine particles are mixed and which is arranged in an optional small compartment is conveyed by said conveyance means in the another liquid filling in the processing means while maintaining a single optional droplet in the another liquid, by passing through each bulkhead separating one small compartment from another.

However, Mehta teaches (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (*the bulkheads are considered as the pillars that separate each retention region*). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210 (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that Mehta teaches the bulkheads on the bottom portion of their channel, however the examiner recognizes that obviousness may be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Mehta teaches that bulkheads and compartments may be incorporated into a channel to assist in separating out magnetic particles from a stream (*column 3 lines 3-35*). It is expected that the same would result if the bulkheads were situated at any side of the channel including the top, as the critical functional feature relies on the depth between the channel and bulkhead's top surface.

Thus it would have been obvious at the time of the invention to arrange Mehta's bulkheads at the top of the channel of Blankenstein because the modification is an aesthetic choice, or a mere rearrangement of an element without modification of the operation of the device. One would have been motivated to arrange the bulkheads on the top of the device to collect the particles at the top portion of the channel. Blankenstein teaches the magnet at the top portion of the channel (figure 1), thus it would have been obvious to have the bulkheads at the top of the channel in order for the magnetic particles to attract to the top portion of the wall and allow the particle-free fluid to flow underneath.

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

Blankenstein does not teach the magnet or conveyance means moving in a direction while applying a magnetic field, rather the magnet (8) is stationary as it's applying the magnetic field.

In the analogous art of particle separation in fluids, Ishiguro teaches a magnet that translate (*magnet 13, figure 3, [0011]*) rightward in the fluidic apparatus that moves

magnetic fluid that was introduced into microchannels (3) towards capacity portions (1, 2), for the benefit of driving magnetic particles across a distance within a channel.

It would have been obvious to one of ordinary skill in the art to use a moving magnet of Ishiguro in the apparatus of Blankenstein because the modification would allow the magnetic particles to move across a further distance within a channel ([0011]).

Regarding claim 18, Blankenstein teaches a fluid out of said plural kinds to which said magnetic ultrafine particles are mixed and which is conveyed to said other small compartments (*the chamber of outlet 6 is where the magnetically stained particles are transferred, figure 1*) where fluid and said magnetic ultrafine particles are mixed and separated (*separation occurs after magnet 8 toward sort outlet 6, figure 1*).

Blankenstein does not teach by said conveyance means by passing through each bulkhead separating one small compartment from another to a droplet that includes said magnetic ultrafine particles and the droplet that does not include said magnetic ultrafine particles by using physical and chemical characteristics such as wettability and surface tension of said optional droplet.

However, Mehta teaches in column 16 line 55 - column 17 line 5, an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (*the bulkheads are considered as the pillars that separate each retention region*). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and

separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

It is noted that the optional language in the claim (i.e. "optional droplet" and "optional compartment") indicates that the feature does not have to be present in order to practice the claimed invention. Further, Blankenstein recites up to three liquids and Mehta discloses multiple compartments separated by bulkheads.

Regarding claim 19, Blankenstein teaches controlling the magnetic field which is externally applied to the droplet to which said magnetic ultrafine particles are mixed, said magnetic ultrafine particles are dispersed and cohered in the inside of the fluid, and also the operations for processing of chemical analysis of the droplet to which said magnetic ultrafine particles are mixed are performed. (*Column 3 line 65 – column 4 line 10 & column 5 line 60-65, column 6 line 20-35, & column 9 lines 10-40*).

Regarding claim 20, Blankenstein does not teach the physical and chemical reaction control by light, heat or pH is used.

However, Mehta teaches in (*column 5 lines 10-15*) teaches a control system that directs a plurality of mixings of the first reactant and the array wherein a reaction condition selected from temperature, pH, and time is systematically varied in separate mixings reactions. Other optional elements include a temperature control element for controlling temperature of reaction of the first and second element, a source of acid, a source of base and a source of reactants, reagents, array members, or the like (*column 5 lines 15-20*).

Therefore it would have been obvious to control the physical and chemical reaction conditions by heat, light, or pH, since the energy provided by these means are known to control the conditions of the reactions (*column 5 lines 15-20*).

Regarding claim 21, Blankenstein in the condition where a specimen for performing chemical reactive operation adhered (*magnetically stained particles, column 3 line 67 column 4 line 9*) to surfaces of said magnetic ultrafine particles, said magnetic ultrafine particles are used as a carrier to perform the chemical reactive operation to said specimen (*column 13 lines 1-15*).

Regarding claims 22, Blankenstein does not teach combining a plurality of said small compartments which are separated by plural bulkheads and which become said processing means, at least a series of chemical reactive operation by reaction, separation and dilution to a specimen that adhered to surfaces of said magnetic ultrafine particles is performed.

However, Mehta teaches in (*column 16 line 55 - column 17 line 5*), an array of flowable or fixed particles sets used in microfluidic systems where in a region of channel 210, several particle retention regions 220-250 (the bulkheads are considered as the pillars that separate each retention region). Particles sets 260-290, which can comprise magnetic beads (*column 3 line 4*) movable by a proximate magnet control applying a magnetic field (*column 11 lines 1-5*) which are retained in the retention region, but communicated to neighboring regions by the narrow portion of channel 210, which fluid without the magnet particles flow through, (*See figure 2A*) for localizing the particles that have adhered to target cells or analytes and separating them from the fluid, thus providing methods for sequencing nucleic acids (*column 3 lines 3-35*).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add protrusion elements such as the bulkheads taught by Mehta in the fluidic system of Blankenstein to retain the magnetic beads or particles and separate them from the fluid, which can provide methods for sequencing nucleic acids (*column 3 lines 3-35*).

Response to Arguments

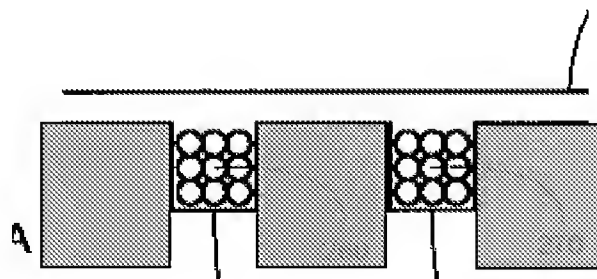
Applicant's arguments filed August 23, 2011 have been fully considered but they are not persuasive.

Applicant argues on page 13 second paragraph that Blankenstein does not teach or suggest droplets containing magnetic ultrafine particles conveyed through a stationary liquid. Although the Examiner acknowledges that Blankenstein does not

explicitly teach droplets, The Examiner respectfully disagrees that Blankenstein should be ruled out as prior art. The term "droplet" does not add weight to the apparatus claim since "Expressions relating the apparatus to contents thereof during an intended operation are of no significance in determining patentability of the apparatus claim." Ex parte Thibault, 164 USPQ 666, 667 (Bd. App. 1969). Furthermore, "[i]nclusion of material or article worked upon by a structure being claimed does not impart patentability to the claims." See *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935) (as restated in *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963)) (see MPEP § 2115).

Applicant argues on page 13 2nd-3rd paragraph that Blankenstein teaches away from the claimed invention because the magnet is fixed and buffer streams 10 and 11 enter the flow channel 5 with the magnetically stained particles. In regards to the fixed magnet, Ishiguro is relied upon for the teaching of a mobile magnet that drives magnetic particles over a long distance within a channel. Thus the combination of Blankenstein and Ishiguro teach the structural limitations of the claimed invention.

Applicant argues on page 14 1st paragraph that Mehta discloses particle retention regions retaining particles sets by a magnetic force and are not analogous to the bulkheads projecting into a processing means from a tip side to form plural small compartments. The Examiner respectfully disagrees. The retention regions are considered as the small compartment created by the side walls, or bulkheads. (See replicated image below, the gray portion is considered as the bulkhead.



The limitation that the bulkheads are situated at the top of the channel is an obvious rearrangement of parts. It is expected that the bulkheads would function the

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same if they are at the top of the bottom of the channel, because the function relies on the different dimensions of the channel and retention region rather than direction (column 16 lines 61-62). Therefore, Mehta teaches on of ordinary skill in the art that bulkheads and retention regions are capable of retaining particles from the fluid stream and it would have been obvious to modify Blankenstein with the bulkheads of Mehta because the modification would allow separation of magnetic particles from a stream where the magnetic particles may have an analyte adhered onto.

Applicant argues on page 15 that Ishiguro merely discloses that the magnetic fluid is introduced into the microchannels by a moving magnet and in combination with the aforementioned references do not teach or suggest the claimed invention. The Examiner respectfully disagrees. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Ishiguro teaches on of ordinary skill in the art that a mobile magnet will attract magnet particles within a channel and carry the particles through the length of the channel when the magnet is moved. Therefore, it would have been obvious to one having ordinary skill in the art to modify the apparatus of Blankenstein with a moving magnet as taught by Ishiguro because the modification would allow magnetic particles to travel across a long channel ([0011]).

The arguments directed to the method claims are not addressed since the method claims are not considered due to election by original presentation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON PREGLER whose telephone number is (571)270-5051. The examiner can normally be reached on Mon - Fri 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, In Suk Bullock can be reached on (571)272-5954. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Pregler/
Examiner, Art Unit 1772

/In Suk Bullock/
Supervisory Patent Examiner, Art Unit 1772